

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:

0.26 - 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix.

After reconstitution with the solvent provided, the concentration of cetrorelix is 0.25 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 0.25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide 0.25 mg should only be prescribed by a specialist experienced in this field.

Cetrotide 0.25 mg is for subcutaneous injection into the lower abdominal wall.

The first administration of Cetrotide should be performed under the supervision of a physician. The following injections may be self-administered as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention.

For instructions for use and handling, see section 6.6.

The contents of 1 vial (0.25 mg cetrorelix) are to be administered once daily, at 24 h intervals, either in the morning or in the evening. Following the first administration, it is advised that the patient be kept under medical supervision to ensure there is no hypersensitivity reaction to the injection.

Administration in the morning: Treatment with Cetrotide 0.25 mg should commence on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with Cetrotide 0.25 mg should commence on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

4.3 Contraindications

- Hypersensitivity to cetrorelix acetate or any structural analogues of GnRH, extrinsic peptide hormones or mannitol.
- Pregnancy and lactation.
- Postmenopausal women.
- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and special precautions for use

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrotide is not advised in women with severe allergic conditions.

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre's practice.

There is limited experience up to now with the administration of Cetrotide 0.25 mg during a repeated ovarian stimulation procedure. Therefore Cetrotide 0.25 mg should be used in repeated cycles only after a careful risk/benefit evaluation.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

4.6 Pregnancy and lactation

Cetrotide 0.25 mg is not intended to be used during pregnancy and lactation (see section 4.3 „Contraindications“).

Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the drug was administered during the sensitive phase of gestation.

4.7 Effects on ability to drive and use machines

Due to its pharmacological profile cetrorelix is unlikely to impair the patient's ability to drive or to operate machinery.

4.8 Undesirable effects

Local reactions at the injection site (e.g. erythema, swelling and pruritus) have been reported. Usually they were transient in nature and mild intensity. The frequency as reported in clinical trials was 9.4% following multiple injections of 0.25 mg cetrorelix. Rare cases of hypersensitivity reactions including anaphylactoid reactions have also been reported.

Occasionally nausea and headache have been reported.

Occasionally an ovarian hyperstimulation syndrome can occur which is an intrinsic risk of the stimulation procedure (see section 4.4 “Special warnings and precautions for use”).

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: LHRH-Antagonist, ATC code: H01CC02.

Cetrorelix is a luteinising hormone releasing hormone (LHRH) antagonist. LHRH binds to membrane receptors on pituitary cells. Cetrorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetrorelix controls the secretion of gonadotropins (LH and FSH).

Cetrorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetrorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. Following a single dose of 3 mg of cetrorelix a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetrorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetrorelix were fully reversible after termination of treatment.

5.2 Pharmacokinetic properties

The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.

The total plasma clearance and the renal clearance are $1.2 \text{ ml} \times \text{min}^{-1} \times \text{kg}^{-1}$ and $0.1 \text{ ml} \times \text{min}^{-1} \times \text{kg}^{-1}$, respectively. The volume of distribution ($V_{d, \text{area}}$) is $1.1 \text{ l} \times \text{kg}^{-1}$. The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site. The subcutaneous administration of single doses (0.25 mg to 3 mg cetrorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetrorelix. No signs of drug-related local irritation or incompatibility were noted in dogs after intravenous, intra-arterial and paravenous injection when cetrorelix was administered in doses clearly above the intended clinical use in man.

Cetrorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, water for injections

6.2 Incompatibilities

As cetorelix is incompatible with several substances of common parenteral solutions it should be dissolved only by using water for injections.

6.3 Shelf life

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the container in the outer carton.

6.5 Nature and contents of container

Packs with 1 or 7 Type I glass vials each containing 55.7 mg powder for solution for injection sealed with a rubber stopper.

Additionally for each vial the packs contain:

1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 1 ml solvent for parenteral use

1 injection needle (20 gauge)

1 hypodermic injection needle (27 gauge)

2 alcohol swabs.

6.6 Instructions for use, handling, and disposal

Cetrotide 0.25 mg should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 0.23 mg cetorelix.

The solution should be used immediately after reconstitution.

The injection site should be varied daily.

7. MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/001

EU/1/99/100/002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

13 April 1999

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 3 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:

3.12 - 3.24 mg cetrorelix acetate equivalent to 3 mg cetrorelix.

After reconstitution with the solvent provided, the concentration of cetrorelix is 1 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 3 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide 3 mg should only be prescribed by a specialist experienced in this field.

Cetrotide 3 mg is for subcutaneous injection into the lower abdominal wall.

The first administration of Cetrotide should be performed under the supervision of a physician. The following injections may be self-administered as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention.

For instructions for use and handling, see section 6.6.

The contents of 1 vial (3 mg cetrorelix) are to be administered on day 7 of ovarian stimulation (approximately 132 to 144 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins. Following the first administration, it is advised that the patient be kept under medical supervision to ensure there is no hypersensitivity reaction to the injection.

If the follicle growth does not allow ovulation induction on the fifth day after injection of Cetrotide 3 mg, additionally 0.25 mg cetrorelix (Cetrotide 0.25 mg) should be administered once daily beginning 96 hours after the injection of Cetrotide 3 mg until the day of ovulation induction.

4.3 Contraindications

- Hypersensitivity to cetrorelix acetate or any structural analogue of GnRH, extrinsic peptide hormones or mannitol.

- Pregnancy, and lactation.
- Postmenopausal women.
- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and special precautions for use

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrotide is not advised in women with severe allergic conditions.

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre's practice.

There is limited experience up to now with the administration of Cetrotide 3 mg during a repeated ovarian stimulation procedure. Therefore Cetrotide 3 mg should be used in repeated cycles only after a careful risk/benefit evaluation.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

4.6 Pregnancy and lactation

Cetrotide 3 mg is not intended to be used during pregnancy and lactation (see section 4.3 „Contraindications“).

Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the drug was administered during the sensitive phase of gestation.

4.7 Effects on ability to drive and use machines

Due to its pharmacological profile cetrorelix is unlikely to impair the patient's ability to drive or to operate machinery.

4.8 Undesirable effects

Local reactions at the injection site (e.g. erythema, swelling and pruritus) have been reported. Usually they were transient in nature and mild intensity. The frequency as reported in clinical trials was 9.4% following multiple injections of 0.25 mg cetrorelix. Rare cases of hypersensitivity reactions including anaphylactoid reactions have also been reported.

Occasionally nausea and headache have been reported.

Occasionally an ovarian hyperstimulation syndrome can occur which is an intrinsic risk of the stimulation procedure (see section 4.4 “Special warnings and precautions for use”).

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: LHRH-Antagonist, ATC code: H01CC02.

Cetorelix is a luteinising hormone releasing hormone (LHRH) antagonist. LHRH binds to membrane receptors on pituitary cells. Cetorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetorelix controls the secretion of gonadotropins (LH and FSH).

Cetorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetorelix delays the LH surge and consequently ovulation.

In women undergoing ovarian stimulation the duration of action of cetorelix is dose dependent. Following a single dose of 3 mg of cetorelix a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetorelix were fully reversible after termination of treatment.

5.2 Pharmacokinetic properties

The absolute bioavailability of cetorelix after subcutaneous administration is about 85%.

The total plasma clearance and the renal clearance are $1.2 \text{ ml} \times \text{min}^{-1} \times \text{kg}^{-1}$ and $0.1 \text{ ml} \times \text{min}^{-1} \times \text{kg}^{-1}$, respectively. The volume of distribution ($V_{d, \text{area}}$) is $1.1 \text{ l} \times \text{kg}^{-1}$. The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site. The subcutaneous administration of single doses (0.25 mg to 3 mg cetorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetorelix. No signs of drug-related local irritation or incompatibility were noted in dogs after intravenous, intra-arterial and paravenous injection when cetorelix was administered in doses clearly above the intended clinical use in man.

Cetorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, water for injections

6.2 Incompatibilities

As cetorelix is incompatible with several substances of common parenteral solutions it should be dissolved only by using water for injections.

6.3 Shelf life

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the container in the outer carton.

6.5 Nature and contents of container

Pack with 1 Type I glass vial containing 167.7 mg powder for solution for injection sealed with a rubber stopper.

Additionally the pack contains:

- 1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 3 ml solvent for parenteral use
- 1 injection needle (20 gauge)
- 1 hypodermic injection needle (27 gauge)
- 2 alcohol swabs.

6.6 Instructions for use, handling, and disposal

Cetrotide 3 mg should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 2.82 mg cetorelix.

The solution should be used immediately after reconstitution.

7. MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/003

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

13 April 1999

10. DATE OF REVISION OF THE TEXT

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BOX OF 1 VIAL AND 1 PRE-FILLED SYRINGE****1. NAME OF THE MEDICINAL PRODUCT**

Cetrotide 0.25 mg, powder and solvent for solution for injection.
Cetorelix (as acetate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial with 55.7 mg powder contains:
0.26 – 0.27 mg cetorelix acetate equivalent to 0.25 mg cetorelix.

3. LIST OF EXCIPIENTS

Excipient: Mannitol.
1 pre-filled syringe with solvent contains: 1 ml water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 pre-filled syringe with solvent for parenteral use.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Keep the container in the outer carton.
Reconstitute only with the solvent provided.
Use immediately after reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder:

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/99/100/001

13. MANUFACTURER'S BATCH NUMBER
--

Lot:

Solvent Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BOX OF 7 VIALS AND 7 PRE-FILLED SYRINGES****1. NAME OF THE MEDICINAL PRODUCT**

Cetrotide 0.25 mg, powder and solvent for solution for injection.
Cetorelix (as acetate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial with 55.7 mg powder contains:
0.26 – 0.27 mg cetorelix acetate equivalent to 0.25 mg cetorelix.

3. LIST OF EXCIPIENTS

Excipient: Mannitol.
1 pre-filled syringe with solvent contains: 1 ml water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

7 vials with powder for solution for injection.
7 pre-filled syringes with solvent for parenteral use.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Keep the container in the outer carton.
Reconstitute only with the solvent provided.
Use immediately after reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder:

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/99/100/002

13. MANUFACTURER'S BATCH NUMBER
--

Lot:

Solvent Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS CETROTIDE 0.25 MG VIAL LABEL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Cetrotide 0.25 mg

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

55.7 mg/vial

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS SOLVENT PRE-FILLED SYRINGE LABEL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Water for Injections

Solvent for use with Cetrotide 0.25 mg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

1 ml/pre-filled syringe

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BOX OF 1 VIAL AND 1 PRE-FILLED SYRINGE****1. NAME OF THE MEDICINAL PRODUCT**

Cetrotide 3 mg, powder and solvent for solution for injection.
Cetrorelix (as acetate)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial with 167.7 mg powder contains:
3.12 – 3.24 mg cetrorelix acetate equivalent to 3 mg cetrorelix.

3. LIST OF EXCIPIENTS

Excipient: Mannitol.
1 pre-filled syringe with solvent contains: 3 ml water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 pre-filled syringe with solvent for parenteral use.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Keep the container in the outer carton.
Reconstitute only with the solvent provided.
Use immediately after reconstitution.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder:	Serono Europe Limited 56 Marsh Wall London E14 9TP United Kingdom
---------------------------------	--

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/99/100/003

13. MANUFACTURER'S BATCH NUMBER
--

Lot:
Solvent Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS CETROTIDE 3 MG VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Cetrotide 3 mg

Subcutaneous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

167.7 mg/vial

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS SOLVENT PRE-FILLED SYRINGE LABEL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

Water for Injections

Solvent for use with Cetrotide 3 mg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

3 ml/pre-filled syringe

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Cetrotide is and what it is used for
2. Before you use Cetrotide
3. How to use Cetrotide
4. Possible side effects
5. Storing Cetrotide
6. Further information

Cetrotide 0.25 mg, powder and solvent for solution for injection.
Cetrorelix (as acetate).

- The active substance is cetrorelix acetate, 0.26 – 0.27 mg equivalent to 0.25 mg cetrorelix.
- The other ingredient is mannitol.
- The solvent is Water for Injections.

Marketing authorisation holder: Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

Manufacturer: Baxter Oncology GmbH
Daimlerstraße 40
60314 Frankfurt
Germany

1. WHAT CETROTIDE IS AND WHAT IT IS USED FOR

Cetrotide 0.25 mg is a powder for solution for injection. It is available in packs of one or seven vials.

Additionally, for each vial the packs contain

- one pre-filled syringe with solvent (water for injections) for parenteral use for dissolving the powder in the vial
- one injection needle with a yellow mark for injecting the water into the vial and withdrawing the solution from the vial
- one injection needle with a grey mark for injecting the solution
- two alcohol swabs for cleaning purposes.

Cetrotide 0.25 mg inhibits the effects of a natural hormone, called luteinising hormone releasing hormone (LHRH). LHRH regulates the secretion of another hormone, called luteinising hormone (LH), which induces ovulation during the menstrual cycle. Cetrotide 0.25 mg inhibits premature ovulation which is undesirable during hormone treatment for ovarian stimulation as only mature egg cells are suitable for fertilisation.

Therapeutic indications

Cetrotide 0.25 mg is used to prevent premature ovulation during a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 0.25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle stimulating hormone (FSH) suggested similar efficacy. HMG and FSH are hormones promoting egg maturation.

2. BEFORE YOU USE CETROTIDE

Do not use Cetrotide:

- if you are allergic to cetrorelix acetate, mannitol or exogenous peptide hormones (medicines similar to Cetrotide 0.25 mg).
- if you are pregnant or breast-feeding
- if you have already reached your menopause
- if you have a moderate or severe kidney or liver disease.

Take special care with Cetrotide:

Special care should be taken in women with an active allergic condition or a known history of allergy. Since treatment with Cetrotide is not advised in women with severe allergic conditions it is important that you inform your doctor of any allergies.

During or following hormonal stimulation of the ovaries an ovarian hyperstimulation syndrome can occur. This event is related to the stimulation procedure with gonadotropins (hormones promoting egg maturation). For symptoms and suitable measures please refer to the Patient Information Leaflet of the gonadotropin-containing medicine prescribed for you.

Luteal phase support (a measure to support the onset of pregnancy) should be given according to the reproductive medical centre's practice.

There is limited experience up to now with the administration of Cetrotide 0.25 mg during a repeated ovarian stimulation procedure. Therefore you should use Cetrotide 0.25 mg in repeated cycles only after a careful risk/benefit evaluation by your doctor.

Pregnancy and breast-feeding:

You should not use Cetrotide 0.25 mg if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.

Driving and using machines:

As far as it is known, Cetrotide 0.25 mg does not impair your ability to drive or to operate machinery.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Experimental investigations have shown that interactions are unlikely with medications that are metabolised in the liver. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

3. HOW TO USE CETROTIDE

How much Cetrotide should you use and how often should you use it?

The following statements apply to Cetrotide 0.25 mg unless otherwise prescribed by your doctor. Please observe these instructions for use, otherwise you will not fully benefit from Cetrotide 0.25 mg.

The contents of one vial (0.25 mg Cetrotide) are to be administered once daily, at 24 h intervals, either in the morning or in the evening.

Administration in the morning: Treatment with Cetrotide 0.25 mg should begin on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with Cetrotide 0.25 mg should begin on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

How should Cetrotide be administered?

The first injection of Cetrotide should be supervised by your doctor. You can carry out the following injections yourself as long as you have been made aware by your doctor of the symptoms that may indicate allergy, the consequences of such a reaction and the need for immediate treatment.

Cetrotide 0.25 mg is for injection under the skin of the lower abdominal wall, preferably around the navel. To minimise local irritation, please select a different injection site each day.

Dissolve Cetrotide 0.25 mg powder only with the water contained in the pre-filled syringe. Do not use a Cetrotide 0.25 mg solution if it contains particles or if it is not clear.

Before you administer Cetrotide yourself, please read the following instructions carefully:

1. Wash your hands. It is important that your hands and all items you use are as clean as possible.
2. Lay out on a clean surface everything you need (one vial, one pre-filled syringe, one injection needle with a yellow mark, one injection needle with a grey mark and two alcohol swabs).
3. Flip off the plastic cover of the vial. Wipe the aluminium ring and the rubber stopper with an alcohol swab.
4. Take the injection needle with the yellow mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Put the needle on the syringe and remove the cover of the needle.
5. Push the needle through the centre of the rubber stopper of the vial. Inject the water into the vial by slowly pushing the plunger of the syringe.
6. Leave the syringe on the vial. Gently agitate the vial until the solution is clear and without residue. Avoid forming bubbles during dissolution.
7. Draw the whole contents of the vial into the syringe. If solution is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.

8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Put the needle on the syringe and remove the cover of the needle.
9. Invert the syringe and push the plunger until all air bubbles have been expelled. Do not touch the needle or allow the needle to touch any surface.
10. Choose an injection site at the lower abdominal wall, preferably around the navel. Take the second alcohol swab and clean the skin at the injection site. Hold the syringe in one hand. Gently pinch up the skin surrounding the site of injection and hold firmly with the other hand.
11. Hold the syringe as you would hold a pencil, insert the needle completely into the skin at an angle of about 45 degree.
12. Once the needle has been inserted completely, release your grasp of the skin.
13. Pull back gently the plunger of the syringe. If blood appears continue as described in step 14. If no blood appears, inject the solution slowly by pushing the plunger gently forward. After all of the solution is injected, withdraw the needle slowly, applying gentle pressure with the alcohol swab on the skin where the needle was inserted. Withdraw the needle at the same angle as it was inserted.
14. If blood appears, withdraw the needle with the syringe and gently apply pressure to the injection site. Do not use this solution but empty the syringe in a sink. Start again with step 1.
15. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury).

If you use more Cetrotide than you should:

Overdosage of Cetrotide 0.25 mg may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects. Therefore, in case of overdosage no specific measures are required.

If you forget to take Cetrotide:

If you forgot to take Cetrotide 0.25 mg on one day, please contact your doctor immediately and ask for advice.

Ideally Cetrotide 0.25 mg should be administered at 24 hours intervals. But if you missed to administer Cetrotide 0.25 mg at the right time it is no problem to administer this dose at a different time of the same day.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cetrotide can have side effects.

Mild and transient reactions may occur at the injection site like reddening, itching, and swelling.

Rare cases of severe generalised allergic reactions have also been reported.

Occasionally systemic side effects, like nausea and headache have been reported. In addition, a single case of pruritus has been reported during treatment with Cetrotide.

Occasionally, stimulation of ovaries with gonadotropins (hormones promoting egg maturation) may lead to a so-called ovarian hyperstimulation syndrome (OHSS). Symptoms like abdominal pain,

tension, nausea, vomiting, diarrhoea and breathing difficulties may indicate an OHSS. Please inform your doctor immediately, if you feel such symptoms.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING CETROTIDE

Keep out of the reach and sight of children.

Do not store above 25°C.

Keep the container in the outer carton in order to protect from light.

The Cetrotide 0.25 mg powder in the vial and the solvent in the pre-filled syringe have the same expiry date. It is printed on the labels and on the carton. Do not use after the expiry date stated on the label or the carton.

The solution should be used immediately after preparation.

Do not use Cetrotide if you notice any visible signs of deterioration.

If you have any further questions please consult your doctor or pharmacist.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Cetrotide is and what it is used for
2. Before you use Cetrotide
5. How to use Cetrotide
6. Possible side effects
5. Storing Cetrotide
6. Further information

Cetrotide 3 mg, powder and solvent for solution for injection.
Cetorelix (as acetate).

- The active substance is cetorelix acetate, 3.12 – 3.24 mg equivalent to 3 mg cetorelix.
- The other ingredient is mannitol.
- The solvent is Water for Injections.

Marketing authorisation holder: Serono Europe Limited
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Manufacturer: Baxter Oncology GmbH
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Germany

1. WHAT CETROTIDE IS AND WHAT IT IS USED FOR

Cetrotide 3 mg is a powder for solution for injection. It is available in a pack with one vial.

Additionally the pack contains

- one pre-filled syringe with solvent (water for injections) for parenteral use for dissolving the powder in the vial
- one injection needle with a yellow mark for injecting the water into the vial and withdrawing the solution from the vial
- one injection needle with a grey mark for injecting the solution
- two alcohol swabs for cleaning purposes.

Cetrotide 3 mg inhibits the effects of a natural hormone, called luteinising hormone releasing hormone (LHRH). LHRH regulates the secretion of another hormone, called luteinising hormone (LH), which induces ovulation during the menstrual cycle. Cetrotide 3 mg inhibits premature ovulation which is undesirable during hormone treatment for ovarian stimulation as only mature egg cells are suitable for fertilisation.

Therapeutic indications

Cetrotide 3 mg is used to prevent premature ovulation during a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 3 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle stimulating hormone (FSH) suggested similar efficacy. HMG and FSH are hormones promoting egg maturation.

2. BEFORE YOU USE CETROTIDE

Do not use Cetrotide:

- if you are allergic to cetrorelix acetate, mannitol or exogenous peptide hormones (medicines similar to Cetrotide 3 mg).
- if you are pregnant or breast-feeding
- if you have already reached your menopause
- if you have a moderate or severe kidney or liver disease.

Take special care with Cetrotide:

Special care should be taken in women with an active allergic condition or a known history of allergy. Since treatment with Cetrotide is not advised in women with severe allergic conditions it is important that you inform your doctor of any allergies.

During or following hormonal stimulation of the ovaries an ovarian hyperstimulation syndrome can occur. This event is related to the stimulation procedure with gonadotropins (hormones promoting egg maturation). For symptoms and suitable measures please refer to the Patient Information Leaflet of the gonadotropin-containing medicine prescribed for you.

Luteal phase support (a measure to support the onset of pregnancy) should be given according to the reproductive medical centre's practice.

There is limited experience up to now with the administration of Cetrotide 3 mg during a repeated ovarian stimulation procedure. Therefore you should use Cetrotide 3 mg in repeated cycles only after a careful risk/benefit evaluation by your doctor.

Pregnancy and breast-feeding:

You should not use Cetrotide 3 mg if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.

Driving and using machines:

As far as it is known, Cetrotide 3 mg does not impair your ability to drive or to operate machinery.

Using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Experimental investigations have shown that interactions are unlikely with medications that are metabolised in the liver. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

3. HOW TO USE CETROTIDE

How much Cetrotide should you use and how often should you use it?

The following statements apply to Cetrotide 3 mg unless otherwise prescribed by your doctor. Please observe these instructions for use, otherwise you will not fully benefit from Cetrotide 3 mg.

The contents of 1 vial (3 mg cetrorelix) are to be administered on day 7 of ovarian stimulation (approximately 132 to 144 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins.

A single dose of Cetrotide 3 mg results in a duration of action of at least 4 days. If the follicle growth does not allow ovulation induction on the fifth day after injection of Cetrotide 3 mg, additionally 0.25 mg cetrorelix (Cetrotide 0.25 mg) should be administered once daily beginning 96 hours after the injection of Cetrotide 3 mg until the day of ovulation induction.

How should Cetrotide be administered?

The first injection of Cetrotide should be supervised by your doctor. You can carry out the following injections yourself as long as you have been made aware by your doctor of the symptoms that may indicate allergy, the consequences of such a reaction and the need for immediate treatment.

Cetrotide 3 mg is for injection under the skin of the lower abdominal wall, preferably around the navel.

Dissolve Cetrotide 3 mg powder only with the water contained in the pre-filled syringe. Do not use a Cetrotide 3 mg solution if it contains particles or if it is not clear.

Before you administer Cetrotide yourself, please read the following instructions carefully:

1. Wash your hands. It is important that your hands and all items you use are as clean as possible.
2. Lay out on a clean surface everything you need (one vial, one pre-filled syringe, one injection needle with a yellow mark, one injection needle with a grey mark and two alcohol swabs).
3. Flip off the plastic cover of the vial. Wipe the aluminium ring and the rubber stopper with an alcohol swab.
4. Take the injection needle with the yellow mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Put the needle on the syringe and remove the cover of the needle.
5. Push the needle through the centre of the rubber stopper of the vial. Inject the water into the vial by slowly pushing the plunger of the syringe.
6. Leave the syringe on the vial. Gently agitate the vial until the solution is clear and without residue. Avoid forming bubbles during dissolution.
7. Draw the whole contents of the vial into the syringe. If solution is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.
8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Put the needle on the syringe and remove the cover of the needle.

9. Invert the syringe and push the plunger until all air bubbles have been expelled. Do not touch the needle or allow the needle to touch any surface.
10. Choose an injection site at the lower abdominal wall, preferably around the navel. Take the second alcohol swab and clean the skin at the injection site. Hold the syringe in one hand. Gently pinch up the skin surrounding the site of injection and hold firmly with the other hand.
11. Hold the syringe as you would hold a pencil, insert the needle completely into the skin at an angle of about 45 degree.
12. Once the needle has been inserted completely, release your grasp of the skin.
13. Pull back gently the plunger of the syringe. If blood appears continue as described in step 14. If no blood appears, inject the solution slowly by pushing the plunger gently forward. After all of the solution is injected, withdraw the needle slowly, applying gentle pressure with the alcohol swab on the skin where the needle was inserted. Withdraw the needle at the same angle as it was inserted.
14. If blood appears, withdraw the needle with the syringe and gently apply pressure to the injection site. Do not use this solution but empty the syringe in a sink.
15. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury).

If you use more Cetrotide than you should:

Overdosage of Cetrotide 3 mg may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects. Therefore, in case of overdosage no specific measures are required.

If you forget to take Cetrotide:

If you forgot to take Cetrotide 3 mg, please contact your doctor immediately and ask for advice.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cetrotide can have side effects.

Mild and transient reactions may occur at the injection site like reddening, itching, and swelling.

Rare cases of severe generalised allergic reactions have also been reported.

Occasionally systemic side effects, like nausea and headache have been reported. In addition, a single case of pruritus has been reported during treatment with Cetrotide.

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If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING CETROTIDE

Keep out of the reach and sight of children.

Do not store above 25°C.

Keep the container in the outer carton in order to protect from light.

The Cetrotide 3 mg powder in the vial and the solvent in the pre-filled syringe have the same expiry date. It is printed on the labels and on the carton. Do not use after the expiry date stated on the label or the carton.

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If you have any further questions please consult your doctor or pharmacist.

6. FURTHER INFORMATION

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